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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,851	09/19/2003	Peter Bodine	00630/100M091-US2	6790

32801 7590 04/15/2008

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
04/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,851	BODINE, PETER	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-43* is/are pending in the application.

4a) Of the above claim(s) *7-19 and 26-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/169,545.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq. alignment*.

DETAILED ACTION

Response to Amendment

Applicant's amendments of the claims received on 19 June 2007 and the specification received on 27 September 2007 have been entered.

Claim 5 has been cancelled. Claims 1-4 and 6-43 are pending. Claims 7-19 and 26-43 are withdrawn from further consideration as being drawn to a nonelected invention. Claims 1-4, 6 and 20-25 are under examination.

Specification

The Application No: 10/169,545 is now patented. The first line of the specification should include updated cross-reference to related applications.

Claim Rejections Withdrawn

The rejection of claim 2 under 35 U.S.C. 103(a), as being unpatentable over Umansky et al. (U. S. Patent No: 6,433,155B1), in view of Warman et al. (WO 02/16553 A2), is withdrawn in response to Applicant's amendment of the claims.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended claims 20-24 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for: *a pharmaceutical composition for regulating bone-forming activity in a mammal comprising an antibody generated using the sFRP-1 of SEQ ID NO: 2, which is encoded by the polynucleotide of SEQ ID NO: 1, or using the fragment of sFRP-1 of amino acids 217-231 of SEQ ID NO: 2, as an immunogen, and wherein the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1,* does not reasonably provide enablement for pharmaceutical compositions comprising antibodies generated using any portions of sFRP-1, for reasons made of record in the previous office actions.

Applicant argues that claim 20 has been amended to recite "at least one antibody generated using an sFRP-1 of SEQ ID NO: 2 as an immunogen and wherein the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1", and claims 22-24 have been similarly amended to recite that the antibody is generated using specific fragments of sFRP-1 protein of SEQ ID NO: 2 as an immunogen. Applicant argues that the specification is enabled for generating an antibody using an sFRP-1 of SEQ ID NO:2, or the specified fragments as an immunogen and require that the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: I (Example 12). Applicant argues that anyone skilled in the art is capable of generating similar antibodies as claimed, using the specified protein fragments followed by

screening for the desired ability of inhibiting cell death mediated by overexpression of the claimed sFRP-1 polynucleotide sequence, as described in the specification.

Applicants' argument has been fully considered but has not been found to be persuasive.

The amended claims are directed a pharmaceutical composition for regulating bone-forming activity in a mammal comprising at least one antibody generated using an sFRP-1 protein of SEQ ID NO: 2, or regulating portion thereof, as an immunogen; wherein the immunogen has at least 8 or 10 consecutive amino acids, or at least amino acids 217-231 of an sFRP-1 protein of SEQ ID NO: 2; and wherein the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1.

The claims are broad in that they encompass and require the use of antibodies that are generated using any portion of an sFRP-1 protein, and these antibodies exhibit the activity of inhibiting cell death mediated by overexpression of sFRP-1, and can be used therapeutically for regulating bone-forming activity in a mammal. As set forth previously, the specification discloses the sFRP-1 protein of SEQ ID NO: 2, encoded by the polynucleotide of SEQ ID NO: 1, and the specification discloses that overexpression of sFRP-1 accelerates human osteoblast cell death (Example 12). The specification discloses that an anti-peptide antisera generated using amino acids 217-231 of sFRP-1 as an immunogen inhibited cell death mediated by overexpression of this gene, e.g., 50-60% of the cells alive after 3 days treatment with the antisera compared to 20-30% of the cells alive in the control group (Example 14 and Fig. 12). The specification,

however, does not provide sufficient support that antibodies generated using any portion of sFRP-1 can have the specific antigen binding activity and exhibit the recited inhibitory activity. Further, the portion of the amino acids 217-231 is present in other protein, i.e., human breast tumor-associated protein 38 (Specht et al., DE19813835-A1, reference provided previously). The specification has not provided support for other fragments, except the amino acids 217-231 of SEQ ID NO: 2. Tandon et al. (Proceedings of the 2005 IEEE Computational Systems Bioinformatics Conference Workshops, 11 August 2005, pages133- 134) teach that identification of epitopes on proteins is of vital importance for antibody production, and that predicting epitopes and non-epitope regions using algorithms based on certain protein properties, such as hydrophilicity, flexibility/mobility, turns and bends, have been developed, but report poor accuracy ranging from 40-60% (see Introduction). Therefore, without guidance for the detailed chemical structure for the immunogens, one of skill in the art would evaluate a large number of non-exemplified portions and fragments of sFRP-1 and determining the efficacy of the antibodies generated by using these immunogens in inhibiting cell death mediated by overexpression of sFRP-1, and in therapeutic uses for regulating bone-forming activity in a mammal. Applicant asserts that anyone skilled in the art is capable of generating the antibodies as claimed, and screening for the desired ability. However, the enablement requirement of 35 U.S.C. 112, first paragraph stipulates one of ordinary skill in the art to make and use the invention, rather than "make and test". The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Therefore, without undue experimentation, one skilled in the art would not know how to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The amended claims 20-24 remain rejected under 35 U.S.C. 102(e) as being anticipated by Umansky et al. (U. S. Patent No: 6,433,155B1) for reasons of record in the previous office action.

Applicant argues that claim 20 has been amended to recite "at least one antibody generated using an sFRP-1 of SEQ ID NO: 2, or regulating portion thereof, as an immunogen, and that the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1", and claims 22- 24 have been amended to recite that the antibody is generated using specific fragments of sFRP-1 protein of SEQ 1D NO: 2. Applicant argues that the SARP proteins described by Umansky are not identical to the sFRP-1 protein of SEQ ID NO: 2, and thus, Umansky cannot anticipate antibodies generated using an sFRP-1 protein of SEQ ID NO: 2 as an immunogen. Applicant argues that Umansky does not teach a pharmaceutical composition containing such an antibody for regulating bone-forming

activity in a mammal, and does not teach an antibody that is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1.

Applicants' argument has been fully considered but has not been found to be persuasive.

The claims encompass a pharmaceutical composition comprising at least one antibody generated using a portion of sFRP-1. Umansky teaches a pharmaceutical composition comprising an antibody (including polyclonal and monoclonal antibodies) against a polypeptide of SARP, e.g., SARP-2, also known as sFRP-1. The polypeptide of SARP-2 shares a 99.7% similarity to the SEQ ID NO: 2 of the instant application, and has 100% identity in the amino acid sequence of residues 217-231. Therefore, the antibody composition of Umansky meets the limitations of the instant invention, and inherently possesses the recited function/activity, since the compositions are the same.

The amended claims 20-24 remain rejected under 35 U.S.C. 102(e) as being anticipated by Rubin et al. (U. S. Patent No: 6,479,255B1), for reasons of record in the previous office action.

Applicant argues that the claims have been amended as described above. Applicant argues that the FRP protein described by Rubin is not identical to the sFRP-1 protein of SEQ ID NO: 2, and thus, Rubin cannot anticipate the presently claimed antibodies. Applicant argues that Rubin does not teach a pharmaceutical composition containing such an antibody for regulating bone-forming activity in a mammal, and does

not teach an antibody that is capable of inhibiting cell death mediated by overexpression of sFRP-1.

Applicants' argument has been fully considered but has not been found to be persuasive.

Rubin teaches anti-FRP antibody compositions with polyepitopic and monoclonal specificity (col. 8, lines 18-23). Rubin teaches antibodies raised against full-length or an epitope of FRP polypeptide (col. 14, lines 45-64). Rubin teaches the pharmaceutical use of the antibody, e.g., monitoring the course of a neoplastic condition in a subject (col. 18, lines 21-32). The amino acid sequence of the FRP taught by Rubin has 96.5% local similarity to SEQ ID NO: 2 of the instant application, and has 100% identity in the amino acid sequence of residues 217-231. Therefore, the antibody composition of Rubin meets the limitations of the instant invention, and inherently possesses the recited function/activity, since the compositions are the same.

New Grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 6 and 20-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Rubin et al. (US 2003/0175864 A1, which has a provisional filing date on 29 May 1997).

The claims are directed to: 1) a pharmaceutical composition comprising an antibody generated using a secreted frizzled related protein-1 (sFRP-1) of SEQ ID NO: 2 as an immunogen and an acceptable carrier or diluent for regulating bone-forming activity in a mammal (claims 1 and 6); wherein the sFRP-1 protein has the amino acid sequence obtained by the expression of the polynucleotide sequence set forth in SEQ ID NO: 1 (claim 25); and wherein the bone forming activity is the regulation of bone growth and bone density (claims 3, 4); and 2) a pharmaceutical composition for regulating bone-forming activity in a mammal comprising at least one antibody generated using a sFRP-1 of SEQ ID NO: 2, or regulating portion thereof, as an immunogen and an acceptable carrier or diluent, and wherein the antibody is capable of inhibiting cell death mediated by overexpression of the polynucleotide set forth in SEQ ID NO: 1 (claims 20, 21); wherein the antibody is generated using at least 8 or 10 consecutive amino acids, or at least amino acids 217-231 of an sFRP-1 protein of SEQ ID NO: 2 as an immunogen (claims 22-24).

Rubin et al. teach anti-FRP antibody compositions (including agonist, antagonist, and neutralizing antibodies) [0058]. Rubin et al. teach antibodies raised against full-length recombinant FRP polypeptide [0090]. Rubin et al. teach the pharmaceutical use of the antibody, e.g., monitoring the course of a neoplastic condition in a subject [0107]. Rubin et al. teach the amino acid sequence of the FRP protein identical to the SEQ ID

NO: 2 of the instant application (see sequence alignment). Rubin et al. also teach the polynucleotide sequence encoding the FRP protein. Although the polynucleotide sequence is not identical to SEQ ID NO: 1 of the instant invention, the expression product, however, is identical. While Rubin et al. do not expressly teach that the antibody is capable of inhibiting cell death mediated by overexpression of sFRP-1 gene, and the pharmaceutical composition is for regulating bone-forming activity (bone growth and bone density) in a mammal, this function/activity would reasonably be considered to be inherent to the composition since it has exactly the same components recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). In addition, for the purpose of applying art, the preamble "for regulating bone-forming activity" is not given weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rubin et al. (US 2003/0175864 A1), in view of Chan et al. (J. Biol. Chem., 1992, 267(35):25202-25207).

Rubin et al. teach as set forth above. Rubin, however, does not teach that the FRP protein is from human osteoblast cells (claim 2).

Chan et al. teach the mammalian homologs of the *Drosophila* polarity gene, *frizzled (fz)*, which are widely expressed in mammalian tissues. Chan et al. teach that hormonal induction of Fz proteins in osteoblasts serves to promote intercellular signaling required for functional response such as increased bone resorption (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Rubin et al., with those of Chan et al., to use an FRP protein isolated from human osteoblast cells for generating an anti-FRP antibody. One of ordinary skill in the art would have been motivated to combine the teachings, because Rubin et al. teach that an anti-FRP antibody can be used in a pharmaceutical composition, and Chan et al. teach that mammalian tissues, in particular, osteoblasts, contain such proteins. Therefore, the combined teachings provide a reasonable expectation of successfully preparing the composition.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
April 8, 2008

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646